REMARKS

The above-noted application stands finally rejected in an Office Action mailed October 29, 2007. Per Applicants' request, on Friday December 14, Applicants faxed proposed amended claims for the Examiner's attention. Applicants' Representative then received a follow-up call from the Examiner. Applicants' understanding from the Examiner's phone call was that the amendment from "60% identical" to "90% identical" was favorably received as overcoming the prior art rejections, although Applicants were cautioned that a new search would still be required. Applicants are grateful for the courtesy extended to them by the Examiner.

Applicants, together with a Request for Continued Examination, submit the instant Response. Claim 1 has been amended to more specifically direct the claim to Applicant's invention. The claims now recite that the sequence identity to Applicant's sequences is 90% rather than 60%. This amendment was proposed in the December 14, 2007 document. Support for the instant claim amendment can be seen in the Specification, page 8, line 24.

New claim 95 is presented, directed to herpes simplex viruses effective in the treatment of squamous cell cancer. The proposed amended claim 1 of December 14, 2007 contained this recitation.

Rejections under 35 U.S.C. § 103(a)

1. Nemunaitis in view of Tang et al. and Jacobs et al.

The Examiner has maintained the rejection of claims 1-3, 5-17, 19-28, 33, 36 and 47 under 35 U.S.C. § 103(a), as unpatentable over Nemunaitis in view of Tang et al. and Jacobs et al. for the reasons of record as stated in the Office action mailed on April 24, 2007 and reasons of record in the October 29, 2007 Office action.

The Examiner contends that since SEQ ID NO:22 of Tang et al. is at least 70% identical to instant SEQ ID NO:1, and that Tang et al. teaches that SEQ ID NO:22 can be used as an antisense polynucleotide molecule by placing it into an appropriate vector for downregulation of its target gene expression, it would have been obvious to one of ordinary skill in the art at the time the invention was made to insert the antisense polynucleotide of SEQ ID NO:22 of Tang et al. into the HSV mutant virus vector of Nemunaitis using the recombinant technology of Jacobs et al. with a reasonable expectation of success.

In order to more precisely claim the instant invention, claim 1 has been amended to recite at least about 90% identical to the listed sequences.

Responsive to the rejection, Applicants respectfully submit that a reasonable expectation of success is not provided by Nemunaitis in view of Tang et al. and Jacobs et al., particularly in view of the new Examination guidelines recently published to guide Examiners in making obviousness rejections under the Supreme Court decision in *KSR International Co. v. Teleflex Inc.* See October 10, 2007 Federal Register, Vol. 72, No. 195, p. 57526, entitled, "Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc.*" According to this document, for an "Obvious to Try" rejection, the Examiner must show the Applicants were choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success (see page 57532).

Applicant respectfully submits that the disclosures of Nemunaitis in view of Tang et al. and Jacobs et al. fail to provide the required "a finite number of identified, predictable solutions." Specifically, with respect to Tang et al., this reference provides an almost uncountable number of solutions, such as the 91 named sequences as well as a "laundry list" of generic possible uses for these sequences. Significantly, none of these uses are shown in working examples in Tang et al.

Specifically, Applicants note that Tang et al. teaches a total of 91 nucleic acids (¶0009). The 91 Tang et al. sequences are disclosed as generically useful for "therapeutic, diagnostic or research utilities" (¶0009), including methods for "preventing, treating, or ameliorating" disease by administering polypeptides (¶0023). Generic uses disclosed include "nutritional uses" (¶0138), "cytokine and cell proliferation/differentiation activity" (¶0139), "stem cell growth factor activity" (¶0144), "hematopoiesis regulating activity" (¶0151), "tissue growth activity" (¶0156), "immune stimulating or suppressing activity" (¶0168), "activin/inhibin activity" (¶0184), "chemotactic/chemokinetic activity" (¶0187), "hemostatic and thrombolytic activity" (¶0191), "cancer diagnosis and therapy" (¶0194), "receptor/ligand activity" (¶0200), "drug screening" (¶0205), "assay for receptor activity" (¶0212), "anti-inflammatory activity" (¶0214), "leukemias" (¶0215), and so on.

For generic medical use "cancer diagnosis and therapy", the entirety of Paragraph 0195 is devoted to listing virtually every cancer type known, including adult and pediatric cancers, solid phase tumors, blood cell malignancies, listing lung cancer, breast cancer, gastrointestinal cancer, urologic cancer, malignancies of the female reproductive tract, kidney cancer, brain cancer, bone

cancer, skin cancer. Finally, it is not disclosed whether increased expression or decreased expression of sequences 1-91 are desirable. It is further respectfully noted that with respect to use of SEQ ID NO:22 for the treatment of cancer, the Tang et al. specification also lacks any working examples showing that the viral vector as claimed would deliver the genes encoding the therapeutic products to the appropriate site and that the genes once delivered would be expressed sufficiently to provide adequate product to effect the desired therapy.

It is respectfully submitted, therefore, that Tang et al. teaches an extremely high number of identified solutions, rather than the finite number as required by *KSR*.

Therefore, it is respectfully submitted that under the new *KSR* guidelines, the Tang et al. reference does not provide the Applicants with "a finite number of identified, predictable solutions, with a reasonable expectation of success." Specifically, 91 named sequences are provided by Tang et al., and at least fourteen major medical uses are disclosed in addition to use for cancer therapy. For the medical use cancer therapy, the 91 sequences are identified as being useful for a listing of virtually every cancer known to man. Therefore, the reference has provided an almost uncountable number of identified solutions. Not only that, but the identified solutions are not "predictable", also required by *KSR*. The gene therapy/antisense arts are still considered "an unpredictable art," by the U.S. Patent Office, especially with respect to whether a specific antisense construct will have therapeutic effect.

Accordingly, Applicants submit that success for the instant invention, including new claim 95, directed to squamous cell cancer, is not predictable, from the references cited, particularly in view of the very large number of solutions identified by Tang et al. The Examiner is respectfully requested to also consider the lack of predictability in general in the fields of antisense/gene therapy. In summary, success of the instant invention could not be predicted in view of the thousands of so-called "solutions" provided by Tang et al. especially in view of the unpredictability of whether a specific antisense construct will have a therapeutic effect.

Reconsideration is respectfully requested.

2. Toyoizumi et al. in view of Estilo et al. and Jacobs et al.

The Examiner has maintained the rejection of claims 1-3, 5-17, 19-28, 33-36, 42, 44-45, 47, and 90-91 35 U.S.C. § 103(a) as unpatentable over Toyoizumi et al. in view of Estilo et al.

and Jacobs et al. for the reasons as record as stated in the Office action mailed on April 24, 2007 and reasons of record in the October 29, 2007 Office action.

The Examiner contends that Estilo et al. "clearly suggested that reducing SCCRO mRNA expression would reduce the disease progression of squamous cell carcinoma of the oral tongue." The Examiner also states that "antisense molecules had been known in the art for decades by the time the claimed invention was made as the traditional, standard, and conventional means to downregulate target mRNA expression," and the "mutant HSV vectors of Toyoizumi et al. were known to be useful to carry exogenous genes to target tissues/cells for cancer therapy," thus allowing for a "reasonable expectation of success" in making this claimed product.

Applicants dispute that skilled artisan would have a "reasonable expectation of success" from the combination of Toyoizumi et al. in view of Estilo et al. and Jacobs et al. in the instant invention. Applicants incorporate by reference the arguments of record in the August 21, 2007 Response. In the instant Response, Applicants in particular wish to bring to the Examiner's attention a paper that constitutes a "teaching away" from the instant invention, rebutting the Examiner's alleged "reasonable expectation of success" obtainable from the cited references. Specifically, the paper evidences that there was an art-recognized difficulty in attaining stable mRNA transcripts in HSV-infected cells in view of the Vhs nuclease expressed by HSV-infected cells, constituting a "teaching away" from the utility of HSV as a delivery vehicle for antisense.

This paper, Everly et al. (2002) *mRNA Degradation by the Virion Host Shutoff (Vhs) Protein of Herpes Simplex Virus: Genetic and Biochemical Evidence that Vhs is a Nuclease*", J. Virol. 76:8560-8571) (co-submitted with the instant Response in an Information Disclosure Statement), evidences that those with skill would expect that the non-specific mRNA degradation by Vhs protein in HSV-infected cells would interfere with an antisense strategy. Everly et al. exemplifies what was well-known in the field at the priority date, namely, that when HSV infects a cell, it introduces a protein called Vhs (virion host shutoff). Vhs is a structural component of the infecting HSV virion and is responsible for non-specific degradation of mRNA. See page 8560, column 1, second sentence, which states that: "[o]f the posttranscriptional mechanisms, one of the best characterized is the destabilization of host and viral mRNAs by the HSV virion host shutoff (Vhs) protein (UL41)" (emphasis added).

While Toyoizumi et al. does refer to a single group's expression of IL-12 in an HSV, such a transcript is trafficked to ribosomes for peptide expression. In contrast, in order to exert

its effect, an antisense nucleic acid must survive in a cell long enough to find and bind to its mRNA target. A skilled person would reasonably conclude, therefore, that the existence of the Vhs protein and its function as a nuclease would render HSV an ineffective vehicle for delivering antisense nucleic acid. Thus, it is clear that even if a skilled person were to consider using HSV to deliver antisense nucleic acid, he/she would be taught away from trying this by knowledge of existence and transcription of the Vhs protein in HSV-infected cells.

Applicants also point out that the gene therapy arts, specifically, anti-sense therapy delivered through an HSV virus vehicle, is considered an art area that is unpredictable. Therefore, in view of the unpredictability of the art area of the instant invention, namely, antisense gene therapy, together with the art recognized difficulty in attaining stable mRNA transcripts in HSV-infected cells in view of the Vhs nuclease expressed by HSV-infected cells, it is respectfully submitted that Toyoizumi et al. in view of Estilo et al. and Jacobs et al. do not provide the required "expectation of success" for a *prima facie* case of obviousness.

Reconsideration is respectfully requested.

For the reasons set forth above, Applicant respectfully submits the claims as filed are allowable over the art of record and reconsideration and issuance of a notice of allowance are respectfully requested. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefor to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to deposit account No. 19-5117.

Respectfully submitted,

Date: January 24, 2008

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